REMARKS/ARGUMENTS

Claims 38-44, 46-51, and 60 have been examined. Claim 60 has been amended. Claim 38 has been canceled. Re-examination and reconsideration of the claims, as amended, are respectfully requested.

As an initial matter, Applicants request the Examiner's acknowledgement and consideration of the Supplemental Information Disclosure Statement filed April 8, 2004.

Claims 42-44, 46-51, and 60 have been rejected under 35 U.S.C. § 103 as allegedly being unpatentable over U.S. Patent No. 6,774,278 issued to Ragheb et al. in view of U.S. Patent No. 5,283,257 issued to Gregory et al. Claims 38-44, 46-51, and 60 have been rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Gregory et al. alone. Such a rejection is traversed in part and overcome in part as follows.

In order to expedite prosecution of the present case, independent claim 60 has been amended to include the limitation of dependent claim 38. Claim 60 now recites a method for inhibiting restenosis in a blood vessel following recanalization of the blood vessel comprising implanting a vascular prosthesis comprising a scaffold having means thereon for releasing mizoribine in the blood vessel. In particular, mizoribine is released from the prosthesis into the blood vessel at a rate between 5 μg/day to 200 μg/day so as to inhibit smooth muscle cell proliferation, wherein substantial release of mizoribine is delayed for at least one hour following implantation of the prosthesis.

As the Examiner certainly knows and appreciates, *prima facie* obviousness requires that the prior art references, alone or in combination, teach or suggest all the claim limitations. M.P.E.P. § 2143.03; *In re Royka*, 180 U.S.P.Q. 580 (CCPA 1974). In the instant case, the claimed rate and delay of mizoribine release of claim 60 has not been reasonably disclosed or suggested by the Ragheb et al. and/or Gregory et al. references. Secondly, no suggestion or motivation, either in the cited references or in the knowledge generally available to

one of ordinary skill in the art, has been cited by the Examiner for the proposed modifications of the reference teachings so as to produce the claimed invention. M.P.E.P. § 2143.01; *In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988).

As the Examiner has already acknowledged, "Ragheb et al. further lack[s] the use MPA and mizoribine to treat vascular disease and the substantial release of mizoribine is delayed for at least one hour following implantation of the prosthesis." Office Action, page 2. With respect to the Gregory et al. reference, the Examiner states, "Gregory et al. does not disclose expressly the rate of release of mizoribine between 5 microgram/day to 200 microgram/day....and the substantial release of mizoribine is delayed for at least one hour following implantation of the prosthesis." Office Action, page 3. The Examiner however attempts to cure these deficiencies by stating that, "it would have been obvious to one having ordinary skill in the art at the time the invention was made to release mizoribine between 5 microgram/day to 200 microgram/day....and the substantial release of mizoribine is delayed for at least one hour following implantation of the prosthesis, since it has been held that where the general conditions of claims are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art." Office Action, pages 3-4 (emphasis added). Applicants respectfully disagree.

There is no suggestion or motivation, either in the prior art references or in the knowledge generally available to one of ordinary skill in the art, to modify the reference teachings so as to produce the claimed invention. Ragheb et al. fails to identify mizoribine as a therapeutic agent, much less the specific mizoribine release characteristics as claimed. Likewise, the Gregory et al. reference fails to disclose or suggest any release characteristics for mizoribine, let alone the specific release rates for mizoribine as claimed. At best, Gregory et al. describes doses for MPA and some other agents, none of which are mizoribine, in amounts greater by 10,000 fold than those described and claimed in the present application. In particular, Gregory et al. describes using doses in the range of milligrams per kilogram per day, while claim 60 requires in contrast daily dosages in the microgram range (i.e., not exceeding 200 micrograms). Col. 5, lines 32-37. For example, the daily dose in Gregory for an average patient having a weight of

fifty (50) kilograms on MPA would be 2,000 milligrams (based on 40 milligrams of MPA/kg/day), which is equivalent to 2,000,000 micrograms per day. These general conditions fall far in excess, by about 10,000 fold, of yielding the claimed dosage of no more than 200 micrograms per day. A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 U.S.P.Q. 303 (Fed. Cir. 1983).

Applicants further point out that the Examiner bears the initial burden of factually establishing and supporting any *prima facie* conclusion of obviousness. *In re Rinehart*, 189 U.S.P.Q. 143 (CCPA 1976); M.P.E.P. § 2142. If the Examiner does not produce a *prima facie* case, the Applicant is under no obligation to submit evidence of nonobviousness. *Id.* In the instant case, the Examiner has not pointed to any evidence in the Gregory et al. and/or Ragheb et al. references which teaches or suggest the specific mizoribine release rate of 5 µg/day to 200 µg/day, wherein substantial release of mizoribine is delayed for at least one hour following implantation as claimed. See *In re Zurko*, 59 U.S.P.Q.2d 1693 (Fed Cir. 2001) ([I]n a determination of patentability .... the Board cannot simply reach a conclusion based on its own understanding or experience - or on its assessment of what would be basic knowledge or common sense. Rather, the Board must point to some concrete evidence in the record in support of these findings).

Applicants request, if the present rejection is maintained, that the Examiner show or explain where the Gregory et al. and/or Ragheb et al. references provide the requisite motivation to modify the teachings so as to produce Applicants' claimed invention. Absent such a showing, Applicants respectfully request withdrawal of this rejection and allowance of independent claim 60 (and the claims dependent thereon).

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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